Received: 10 May 2021 | Revised: 25 June 2021 | Accepted: 11 July 2021

DOI: 10.1111/ane.13508

Acta Neurologica Scandinavica WILEY

CLINICAL COMMENTARY

Oxygen for seizures, more questions than answers: A scoping review

Alexander Nicholas Smith[1] | Julie Abraham[1] | Rohit Shankar[2]

[1]Royal Cornwall Hospital Truro, University of Exeter Medical School, Cornwall, UK

[2]Cornwall Intellectual Disability Epilepsy Research (CIDER), University of Plymouth Medical School, Truro, UK

Correspondence
Rohit Shankar, Cornwall Intellectual Disability Epilepsy Research (CIDER) University of Plymouth Medical School, Truro, UK.
Email: rohit.shankar@nhs.net

Background: Ictal hypoxaemia is a feature seen in epileptic seizures, characterized by low oxygen saturations, increasing seizure prolongation risk and possibly contributing to sudden unexpected death in epilepsy (SUDEP). High flow oxygen is recommended in the management of seizures by UK's National Institute of Health and Care excellence (NICE); however, the evidence supporting this recommendation is unclear.

Aims: To identify the efficacy of oxygen in the seizure treatment.

Method: A scoping review was conducted using PRISMA-ScR guidance. PsycINFO, EMBASE and MEDLINE were searched along with the references section of identified literature. Articles were critically appraised for study, patient, seizure, oxygen therapy and outcome characteristics, summarized and quality-assessed using Sackett's criteria.

Results: Literature search identified 623 articles of which five met the pre-criteria for full review. One animal study demonstrated favourable effects of oxygen administration. Three human studies also reported favourable effects of oxygen administration, while one reported outcomes that were not statistically significant. Study design concerns in all identified literature confounded the ability to assess efficacy. All five publications were assigned Sackett's score of 2b.

Conclusion: There is a significant lack of evidence to support the efficacy of oxygen administration in epileptic seizures. Future research is needed.

KEYWORDS
epilepsy, hypoxaemia, ictal hypoxaemia, oxygen therapy, seizures

1 | BACKGROUND

Ictal hypoxaemia (IH) is a major cause for concern due to its importance in the life-threatening consequences of seizures. IH is a feature often seen in both focal and generalized seizures.[1] Oxygen saturations <90% are reported during 20%–30% of all seizures, with severe IH defined as an oxygen saturation below 85%.[1,2] Severe IH increases the risk of recurrent desaturation, resulting in longer seizures and a higher risk of sudden unexpected death in epilepsy (SUDEP).[1,2] Seizure-induced cardiorespiratory dysfunction has been recognized as a significant risk factor in SUDEP pathophysiology.[2] This is considered instrumental in the damage and dysfunction to the cortical and subcortical areas responsible for breathing regulation, resulting in seizure-induced central apnoea.[1,2] Consequently, compromise in oxygen and carbon dioxide exchange may occur, resulting in hypoxaemia and hypercapnia.[2] These changes, alongside a variety of other factors, can influence SUDEP occurrence.[3]

At present, the National Institute of Health and Care Excellence (NICE) recommends high flow oxygen use in hospital management of seizures; however, no reference source is provided.[4] Contradicting this guidance, research has shown IH to be a mechanism of seizure termination, meaning oxygen administration may prolong seizures.[5]

It also remains unclear whether peri-ictal oxygen administration is effective in treating the underlying central and obstructive apnoeic aetiology of IH.

1.1 | Aim

The study looks to determine the nature and quality of evidence of oxygen therapy in the treatment of IH in seizures.

1.2 | Methodology

A review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) as guidance (Supporting Information).[6] A literature search of PsycINFO, EMBASE, and MEDLINE was completed to identify articles focussed on oxygen therapy in seizure management in human and animal models. The literature screening process is shown in Figure 1. The search methodology is provided in Appendix 1. Identification of relevant articles, followed by abstract screening and suitability assessment, was undertaken independently by two authors under supervision from the third author. The references section of identified literature was searched for additional papers. No date range was used with the latest search executed in 10/2020. Included articles were written in English, and all involved the use of oxygen therapy in the treatment of seizures in human and animal populations. No exclusions were made relating to other aspects of study design to capture the breadth of literature available. Each selected paper's provenance, study design, participant profile, seizure characteristics, oxygen therapy details, findings, identified bias and limitations was captured. Critical appraisal of each paper's quality was conducted using Sackett's criteria.[7] No ethics were needed as this was a review not a human study.

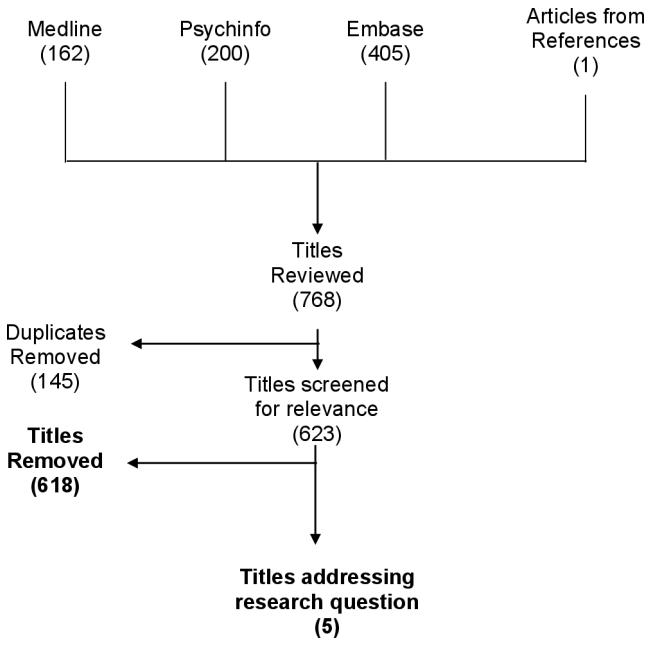

FIGURE 1 The literature screening process

2 | RESULTS

The search yielded 623 articles of which 618 were excluded. Five papers were included in the analysis: four involving human participants and one based on animal models.

Detailed appraisal of each study is provided in Table 1.

Each study achieved Sackett's score of 2b. The animal and three human studies demonstrated favourable outcomes. One human study demonstrated no significant difference between participants who did or not receive oxygen administration.

2.1 | Human models

A prospective cohort study investigated whether early administration of oxygen improved postictal hypoxaemia in 76 patients (107 seizures).[8] The oxygen saturation (SpO2) evolution during seizures and postictal period was measured. The SpO2 nadir, its delay with respect to the end of generalized convulsive seizures (GCS) and occurrence of different severities of hypoxaemia were also assessed. Postictal hypoxaemia without early administration of oxygen lasted 29.9 s longer on average ($p = .035$). Early oxygen administration caused a SpO2 nadir 9.1% higher than those without early administration ($p = .001$), with a delay 6.4 s shorter with respect to the end of seizure ($p < .001$). These results demonstrate postictal hypoxaemia was shorter and less severe in those who received early oxygen administration.

A retrospective cohort study investigated the impact of peri-ictal nurse interventions on postictal generalized electroencephalography suppression (PGES) in 150 GCS in 109 patients.[9] One group ($n = 29$) received ictal oxygen administration, while another ($n = 119$) did not. Differences in seizure variables between groups were not statistically significant, demonstrating that oxygen administration was not linked to changes in seizure activity.

A multicentre prospective cohort study investigated the effect of early oxygen administration on the presence of PGES in 69 patients (99 GCS).[10] The study concluded that PGES was more likely to be present in those who did not receive early oxygen administration in univariate and multivariate analysis ($p < .001$). The study also showed that early oxygen administration is protective against the development of PGES.

A retrospective cohort study was performed investigating the impact of peri-ictal interventions on respiratory dysfunction, PGES and postictal immobility.[11] The study involved 39 patients (105 GCS) that were placed in two groups who either received (INT) or did not receive (NOINT) peri-ictal interventions. Duration of hypoxaemia was shorter in the INT group compared with NOINT when intervention occurred prior to onset of hypoxaemia ($p = .0014$). Earlier intervention was also associated with shorter duration of hypoxaemia

($p < .0001$) and shorter PGES duration ($p = .0012$). The difference in entire seizure duration and individual seizure variables between the INT and NOINT groups was not statistically significant. The results showed that peri-ictal intervention following GCS is associated with reduced duration of respiratory dysfunction and PGES but had no effect on seizure duration and variables.

2.2 | Animal model

A non-randomized controlled trial using various strains of audiogenic-seizure (AGS) susceptible mice ($n = 279$) was conducted.[12] This study assessed the effect of oxygenation on incidence, severity and rate of fatality of AGS. Mice were placed in either a pure oxygen chamber at the time of AGS or in an air chamber as a control and compared against each other. Oxygenation resulted in zero AGS deaths, whereas most mice in air chambers died following AGS due to respiratory arrest. Further testing suggested that oxygenation had no long or short-term protective effect on fatality, incidence or severity of AGS ($p < .01$).

3 | DISCUSSION

A small sample size was used in four identified human studies, reducing their statistical power.[8-11] As a result, the outcomes of oxygen therapy may not be representative of its efficacy in the general population. All studies included high levels of heterogeneity within their study samples. Factors including age of epilepsy onset, seizure type, disease duration, medication and demographics may have introduced bias. In the animal model, variation in mouse strains may have confounded the results due to genetic variability in predisposition to AGS and its potential influence on oxygen efficacy and mortality.[12] The mechanism of AGS in mice and SUDEP in humans may share commonalities, but neither mechanism nor pathophysiology is well understood meaning results cannot be directly applied to human participants.

Further bias may have been introduced in studies which withdrew epileptic medication to induce seizure activity.[8,9] Antiepileptic drug withdrawal can increase occurrence of certain seizure types.[13] These may have a different aetiology of ictal hypoxaemia and therefore impact the efficacy of oxygen therapy. Future research must aim to homogenize study methods in this regard.

Two studies reported outcomes retrospectively.[9,11] This inherently predisposes research to selection bias and relies on pre-existing data to create relevant exposures and outcomes measures.

A significant limitation in three of the studies was the administration of multiple interventions alongside oxygen.[9-11] This prevents the ability to conclude whether outcomes are solely due to oxygen therapy. In two studies, oxygen saturations and respiratory monitoring data were either discarded from use or performed at the discretion of the nursing staff, detracting from the richness of data and introducing the potential for information bias.[9,10]

The type of equipment used to administer oxygen was poorly documented, and where described variation between studies existed.[8-11] One human study commented on saturation sensor detachment occurring in 76 seizures, with an association observed between detachment rate and oximetry sensor type ($p < .05$).[8] This demonstrates the need for consensus on the most appropriate method of oxygen delivery and saturation equipment to use in future research. In all studies, the percentage of oxygen and rate of delivery were not discussed, impeding the ability to replicate findings.

3.1 | Limitations

Despite a robust attempt to capture all relevant literature, some articles may have been missed due to language barriers, lack of access and lack of detailed information to draw valuable conclusions. Search terms used may not have extracted all the relevant literature. Furthermore, the method of reporting outcomes was not always consistent for each study, complicating direct comparison. These factors have limited the potential breadth of literature available for this review, but are unlikely to have compromised its findings.

4 | CONCLUSION

This review highlights a lack of evidence to support oxygen administration during epileptic seizures. The evidence available is limited and suggests mixed outcomes. The study design of identified literature, heterogeneity among participants, lack of detail about oxygen administration, lack of respiratory data recording, limited sample sizes and question over the most appropriate respiratory monitoring hardware to use provide challenges to relying on the evidence. Crucially, human studies often did not investigate administration versus non-administration of oxygen. They usually assessed early/late administration of oxygen in combination with other interventions. Future research should focus on correcting these variations to mitigate the potential for confounding factors.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

Rohit Shankar has received institutional and research support from LivaNova, UCB, Eisai, Veriton Pharma, Bial, Averelle and GW pharma outside the submitted work. No other author has any declared conflict of interest related to this paper.

AUTHOR CONTRIBUTIONS

All substantially contributed to the design, analysis, interpretation of the work, drafting and preparation of the manuscript, and final

TABLE 1 Critical appraisal and summary of identified literature

Paper details	Participant profile	Epilepsy and seizure profile	Oxygen therapy details
Title: Hypoxemia following generalized convulsive seizures (GCS) Year: 2019 Country: USA Type: Multicentre prospective cohort study Citation: Rheims et al. 2019	Demographics: Total number of participants (n = 73) Total number of seizures analysed (n = 107) Age: 34.1 y/o mean, 10.9 years SD Sex: 51%M, 49%F	Type of epilepsy: Drug-resistant focal epilepsy 52% temporal lobe 21% frontal lobe 5% parietal lobe 3% perisylvian/insula 16% multilobar 3% unknown Age of Onset: 15.7 y/o mean, 10.7 years SD Duration: 18.4 y/o mean, 11.5 years SD Type of Seizures Observed: GCS 45% GCS type 1 23% GCS type 2 32% GCS type 3 (Alexandre V, Mercedes B, Valton L, et al. Risk factors of postictal generalized EEG suppression in GCS. Neurology 2015;85:1598–1603.) Raw Data Monitored During Seizures: EEG, video, pulse oximetry and EKG Method of seizure recording: Long-term scalp EEG recordings Diagnosis of Epilepsy: International League Against Epilepsy Classification	Patients split into two groups: those who received early administration of O2 and those who did not receive early administration of O2 Early administration of O2 defined as receiving oxygen with nasal cannulae or mask during the seizure or within the first 5 s after seizure termination Late administration of O2 defined as receiving oxygen with nasal cannulae or mask greater than 5 s after seizure termination Transient hypoxaemia defined as SpO2 < 90% during at least 5 s Moderate and severe hypoxaemia defined as SpO2 ≤80% and ≤70% respectively. Details of oxygen therapy unclear. % of oxygen delivered unclear.

Findings	Bias and limitations	Sackett's score and comments
Improvement measures: Evolution of SpO2 during the course of seizures and postictal period was assessed. Three minutes preceding the seizure, during the seizure and up to 10 min after end of GCS. Primary outcome The duration of postictal hypoxaemia after GCS termination Secondary outcomes 1. Nadir of SpO2 and its delay with respect to end of GCS 2. Occurrence and duration of moderate hypoxaemia (<80% SpO2) and severe hypoxaemia (<70% SpO2) Significant *p* value = <.05 Outcomes: O2 administered early in 42 seizures O2 not administered early in 65 seizures Early recovery of SpO2 ≥ 90% associated with early administration of O2 (*p* = .004) Primary GCS Without early administration of O2 Mean duration of postictal hypoxaemia—71.1 s GCS With early administration of O2 Mean duration of postictal hypoxaemia—41.2 s Comparison between GCS with and without early administration of O2 (*p*-value) Mean duration of postictal hypoxaemia—0.035 Secondary GCS Without early administration of O2 SpO2 nadir—69.6% Delay between end of seizure and SpO2 nadir—16.1 s GCS With early administration of O2 SpO2 nadir—78.7% Delay between end of seizure and SpO2 nadir—9.7 s Comparison between GCS with and without early administration of O2 (*p*-value) SpO2 Nadir—0.001 Delay between end of seizure and SpO2 nadir—<0.001 Rate of GCS with severe hypoxaemia (SpO2 < 70%) dropped from 40% to 21% when O2 given early (*p* = .046) Rate of GCS with moderate hypoxaemia (SpO2 < 80%) dropped from 69% to 43% when O2 given early (*p* = .007) No significant results related to duration of moderate or severe hypoxaemia in either group. Other outcomes: Evolution of SpO2 after GCS termination was associated with localization of epileptogenic zone, with slower recovery to SpO_2 ≥ 90% in temporal lobe seizures Early recovery of SpO_2 ≥ 90% was associated with absence of postictal generalized EEG suppression.	Of 166 GCS in 114 patients with valid SpO2 measurements, only 107 GCS in 73 patients could be used due to technical limitations (movement artefact on trace, removal of pulse oximeter, transient loss of signals and sensor repositioning) of using equipment pulse oximetry equipment which would have confounded results Antiepileptic drug withdrawal may have been performed during recordings to promote occurrence of seizures (?may have confounded results as not an organic seizure?) Unclear % O2 given to each patient Oxygen mask or nasal cannulae delivery given to each patient meaning different oxygen deliveries Different lobes of epileptic seizures may confound results as certain lobes may induce more debilitating seizures which worsen SpO2 evolution Limited sample size Nasal airflow and abdominal respiratory excursions not recorded limiting interpretation of origins of respiratory apnoea	Sackett's score = 2b Mean duration of postictal hypoxaemia significantly reduced with early O2 administration SpO2 nadir significantly less severe with early O2 administration Delay between end of seizure and SpO2 nadir significantly reduced with early O2 administration Rate of transient loss of SpO2 signal and sensor disconnection were associated with type of oximetry sensor (lower rates with disposable flexiform sensors than finger clip sensor or reusable soft sensor Future research must identify the best type of pulse oximetry to use in GCS analysis of hypoxaemia Localization of epileptogenic zone could be done in 71 patients only Must be determined whether or not the therapeutic effect of oxygen administration might be increased through optimization of oxygen delivery protocol Only specific seizure types (focal with bilateral tonic–clonic evolution) included in this study so scope in future studies to examine other epilepsy types Question remains "Is O2 therapy efficacy altered by mechanism of hypoxaemia (different when triggered by central apnoea or obstructive apnoea) Commentary on these articles suggests that providing the patient a suction machine and education on proper GCS intervention may serve better than O2 delivery, but this would need to be given further research (Kotagel p., 2019)

(Continues)

TABLE 1 (Continued)

Paper details	Participant profile	Epilepsy and seizure profile	Oxygen therapy details
Title: Impact of peri-ictal nurse interventions on postictal generalized EEG suppression in GCS Year: 2016 Country: USA Type: Retrospective cohort study Citation: (8)	Demographics: Total number of participants (n = 109) Total number of seizures analysed (n = 150) Age: 35 y/o mean, 14.7 years SD Sex: 44%M, 56%F	Type of Epilepsy: Unknown Age of Onset: Unknown Duration: Unknown Type of Seizures Observed: 21.3% primary GCS 78.6% partial-onset seizures with secondary GCS (GCS, generalized convulsive seizures) Raw Data Monitored During Seizures: PGES presence and duration of the following: PGES, ESD, TCP, TP and CP. Method of seizure recording: Video-EEG recordings using 26 channels Diagnosis of Epilepsy: Unknown	Patients split into two groups, those that received peri-ictal intervention and those that did not Separate analysis comparing patients that did and did not received oxygen administration Oxygen and other ictal interventions given between ictal EEG onset and termination (usually preceding onset of PGES)
Title: Risk factors of postictal generalized EEG suppression in GCS Year: 2015 Country: USA Type: Multicentre prospective cohort study Citation: (9)	Demographics: Total number of participants (n = 69) Total number of seizures analysed (n = 99) Age: PGES: 32.2 y/o mean No PGES: 33.8 y/o mean Sex: PGES: 58%M 36%F No PGES: 42%M 64%F	Type of Epilepsy: Drug-resistant focal epilepsy Age of onset: PGES 16.5 y/o No PGES 11.6 y/o Duration: PGES 15.0 y/o mean No PGES 22.3 y/o mean Type of Seizures Observed: GCS PGES present: GCS type 1—(n = 33) GCS type 2—(n = 4) GCS type 3—(n = 10) PGES absent: GCS type 1—(n = 18) GCS type 2—(n = 23) GCS type 3—(n = 11) Raw Data Monitored During Seizures: Duration of tonic phase, duration of tonic-clonic phase, total seizure duration Method of seizure recording: Long-term scalp EEG recordings Diagnosis of Epilepsy: International League Against Epilepsy Classification	Patients split into two groups, those that experiences PGES and those that did not PGES defined as immediate postictal (within 30 s following seizure termination), generalized and severe attenuation of scalp EEG activity no higher than 10 microvolts in amplitude during greater than or equal to 10 s excluding artefact due to muscle, movements, electrodes and respiration. Early O2 administration defined as patient with oxygen mask during the seizure or within the first 5 s after seizure termination

Findings	Bias and limitations	Sackett's score and comments
Improvement Measures: Analysis of effect of administration of oxygen on entire seizure duration (EDS), tonic-clonic phase duration (TCP), tonic phase duration (TP), clonic phase duration (CP) and PGES duration (PGES). All variables measured in seconds, standard deviation shown to the right of the result in brackets Relevant outcomes: GCS With oxygen administered ($n = 29$): ESD—125.4 s (64.8) TCP—70.1 s (20.5) TP—27.8 s (20.1) CP—42.3 s (19.8) PGES—36.2 s (15.6) GCS Without oxygen administered ($n = 73$): ESD—115.7 s (94.6) TCP—61.5 s (24.3) TP—17.4 s (14.4) CP—44.2 s (23.1) PGES—44.1 s (20.3) No statistically significant results existed when comparing seizure-related variables between groups. Other outcomes: TP in GCS without PGES was 10.4 s shorter than GCS with PGES, this was statistically significant ($p = .00086$) PGES duration was 15.5 s shorter in the group receiving peri-ictal intervention of any kind compared with the group receiving no peri-ictal intervention; this was statistically significant ($p = .003$)	Peri-ictal pulse oximetry only performed at discretion of nursing staff and not consistently measured Formal respiratory monitoring not performed The method of oxygen therapy delivered was not specified Ictal oxygen was administered in 29 GCS, of which 93% received other interventions such as oral suction or body repositioning Effect of oxygen therapy is confounded by effect of other interventions Small number of participants receiving oxygen therapy meaning lack of statistical power Demographics poorly defined, no mention of details of epilepsy diagnosis and what drugs patients were taking Heterogeneous population studied confounding results Peri-ictal interventions may have introduced artefact on the EEG from which seizure-related variables were derived confounding	Sackett's score =2b There may have been reduction or discontinuance of epileptic medication to facilitate recording of habitual seizures EEG recordings excluded if significantly obscured by muscle and electrode artefacts Peri-ictal interventions (oxygen administration, oral suction and body repositioning) performed at discretion of nursing staff meaning bias of who received oxygen therapy was introduced
Improvement Measures: Number and percentage of patients receiving early oxygen administration. Duration of tonic phase, duration of tonic-clonic phase and total seizure duration all measured in seconds. Prone positioning at end of seizure. If early intervention was given (apart from O2 administration). State of wakefulness. Relevant Outcomes: Oxygen administered early in 45 patients (45%) PGES present: Early O2 Administration ($n = 10$) Late O2 Administration ($n = 37$) PGES absent: Early O2 Administration ($n = 35$) Late O2 Administration ($n = 17$) PGES presence was associated with lack of early oxygen administration in univariate and multivariate analysis ($p < .001$) Other Outcomes: Occurrence of PGES was significantly associated with longer duration of tonic phase and type of GCS ($p < .001$)	Details of oxygen therapy administered not discussed Oxygen saturation and other respiratory monitoring data was purposefully discarded in this study Limited sample size Heterogeneity among epilepsy type in population Administration of O2 done alongside interventions such as body positioning and electrode replacement may have confounded the results	Sackett's score = 2b PGES was strongly prevented by early oxygen administration

(Continues)

TABLE 1 (Continued)

Paper details	Participant profile	Epilepsy and seizure profile	Oxygen therapy details
Title: Impact of peri-ictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility Year: 2013 Country: USA Type: Retrospective cohort study Citation: (10)	Demographics: Total number of participants (n = 39) Total number of seizures analysed (n = 104) Age: 35.2 y/o mean, 18–66 y/o range Sex: 51%M 49%F	Type of Epilepsy: Localization-related epilepsy Age of onset: Unknown Duration: Unknown Type of Seizures Observed: Secondarily generalized convulsions Right temporal onset (n = 42) Left temporal onset (n = 32) Near simultaneous bitemporal onset (n = 3) Frontal onset (n = 15) Could not be determined (n = 12) Raw Data Monitored During Seizures: Seizure duration, onset of localization, duration of convulsive component of seizure, pre-ictal baseline SaO2 and ETCO2, time of onset of hypoxaemia (SaO2 drop below 90%), SaO2 nadir, peak ETCO2 during ictal/postictal phases, duration of PGES Method of seizure recording: Video-EEG telemetry Diagnosis of Epilepsy: Unknown	Data analysed in consecutive patients Patients receiving nursing interventions (INT) compared to those that did not receive nursing interventions (NOINT) Two groups compared against duration of PGES and hypoxaemia Analysis to see impact of interventions given prior to onset of hypoxaemia compared to after hypoxaemia onset

Findings	Bias and limitations	Sackett's score and comments
Improvement Measures: Duration of hypoxaemia, total seizure duration, SaO2 desaturation nadir, duration of postictal immobility, ETCO2, PGES duration. Relevant Outcomes: Number of seizures in INT group ($n = 84$) Number of seizures in NOINT group ($n = 21$) INT Breakdown of Interventions: Oxygen administered ($n = 41$) Recumbent lateral positioning (47) Suctioning administered ($n = 65$) Impact of interventions on duration of hypoxaemia No significant difference in the slopes of the three interventions including administration of oxygen versus duration of hypoxaemia ($p = .5316$) Duration of PGES and Seizure Onset Linear regression indicated significant positive linear relationship between time of first intervention relative to seizure onset and duration of PGES ($p = .0012$) Mean duration of hypoxaemia with any intervention prior to hypoxaemia onset Mean 53.1 s ± SD 45.1 s (median 44, range 8–158) Mean duration of hypoxaemia with any intervention after hypoxaemia onset Mean 132.4 s ± SD 134.9 s (median 103, range 38–712) Significant difference in mean duration of hypoxaemia between INT and NOINT ($p < .0001$) Duration of hypoxaemia in NOINT Mean 48.9 ± SD 40.9 s (median 37, range 10–188) Duration of hypoxaemia in INT Mean 110.9 ± SD 93.9 s (median 99, range 8–712) The time of onset of hypoxaemia from seizure onset was not significantly different between the two groups ($p = .3351$).I Interval to onset of hypoxaemia from seizure onset in NOINT Mean 101.6 ± SD 78.3 s (median 77, range 32–317) Interval to onset of hypoxaemia from seizure onset in INT Mean 81.5 ± SD 59.7 s (median 63, range 12–404). Mean O2 desaturation nadir in NOINT compared to INT was statistically significant ($p = .0086$) O2 Desaturation Nadir in NOINT Mean 79.8% ± SD 7.7% (median 83, range 61–91) O2 Desaturation Nadir in INT Mean 72.8% ± SD 11.4% (median 75, range 42–93) The difference in peak ictal/postictal ETCO2 between the two groups was significant ($p = .0359$) Peak ictal/postictal ETCO2 in NOINT Mean 50.3 ± SD 7.1 mmHg (median 51, range 40–61) Peak ictal/postictal ETCO2 in INT Mean 58.6 ± SD 13.1 mm Hg (median 59.5, range 38–94). Intervention of any kind and in any combination given prior to onset of hypoxaemia resulted in shorter duration of hypoxaemia when compared to interventions occurring after hypoxaemia onset ($p = .0014$) SaO2 nadir not significantly different for interventions before and following onset of hypoxaemia Other Outcomes: No significant difference in mean duration of seizure ($p = .3514$) or mean duration of convulsive component ($p = .3971$) between INT and NOINT Duration of postictal immobility was significantly related to lower O2 nadir ($p = .003$) Duration of PGES (occurred in INT group only) Mean 41.6 ± SD 25.3 s (median 36, range 2–117)	Multiple interventions given by nurses meaning pure effect of oxygen administration cannot be determined Retrospective nature of study is a limitation Variance in effectiveness of care given by nurses due to differing experience levels	Sackett's score = 2b

(Continues)

TABLE 1 (Continued)

Paper details	Participant profile	Epilepsy and seizure profile	Oxygen therapy details
Title: Oxygenation prevents sudden death in seizure-prone mice Year: 2004 Country: USA Type: Non-randomized controlled trial Citation: (11)	Demographics: Three different mouse strains (D2, B6SAS and Primed-B6) were used. Each strain had three test groups. Total number of mice used in study (n = 279) Age: D2 and primed-B6 mice tested at age 21 ± 1 day. B6SAS mice tested at age 26 ± 2 days Sex: Mixture of male and female mice used. No data available on specific quantities of male or female mice.	Type of Epilepsy: Audiogenic seizure (AGS) Age of Onset: All mice tested at ages stated previously. Duration: Unknown. Type of Seizures Observed: Audiogenic seizures manifest in three phases: wild running, clonic and tonic seizures. Raw Data Monitored During Seizures: Numeric scores based on severity of seizure observed. Method of seizure recording: Observation. Diagnosis of Epilepsy: Not applicable.	All three strains of mice were divided into three groups, and two more treatment groups were created out of mouse survivors in group two. Treatment group one were mice placed in a normal air chamber for their auditory-induced seizure. Treatment group two were placed in a chamber of medically pure oxygen for their seizure. Treatment group 3, included mice that survived from group 2 and were tested 24 h later in an oxygen chamber. Treatment group 4 included mice that survived from group 2 and were tested 24 h later in an air chamber. Treatment group 5 included mice that were tested in an air chamber 1 min after being exposed to oxygen for 2 min prior

approval of the manuscript, and all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work. All authors meet all four ICMJE criteria for authorship.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are within this submission.

ORCID

Rohit Shankar https://orcid.org/0000-0002-1183-6933

REFERENCES

1. Bruno E, Maira G, Biondi A, Richardson MP. Ictal hypoxaemia: a systematic review and meta-analysis. *Seizure*. 2018;*63*:7-13. https://doi.org/10.1016/j.seizure.2018.10.011
2. Surges R, Sander L, Thijs R. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat Rev Neurol*. 2009;*5*:492-504. https://doi.org/10.1038/nrneurol.2009.118
3. Dlouhy BJ, Gelback BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. *J Neurol Neurosurg Psychiatry*. 2016;*87*:402-413. https://doi.org/10.1136/jnnp-2013-307442
4. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management Clinical guideline [CG137]. 2012. https://www.nice.org.uk/guidance/cg137/chapter/1-guidance#prolonged-or-repeated-seizures-and-convulsive-status-epilepticus-2. Accessed 2 December 2020.
5. Schuele SU, Bermeo AC, Alexopoulos AV, Burgess RC. Anoxia-ischemia: a mechanismofseizureterminationinictalasystole.*Epilepsia*.2010;*51*(1):170-173. https://doi.org/10.1111/j.1528-1167.2009.02168.x
6. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;*169*(7):467-473. https://doi.org/10.7326/M18-0850
7. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1989;*95*(2 Suppl):2S-4S.
8. Rheims S, Alvarez BM, Alexandre V, et al. Hypoxemia following generalized convulsive seizures: risk factors and effect of oxygen therapy. *Neurology*. 2019;*92*(3):183-193. https://doi.org/10.1212/WNL.0000000000006777
9. Wu S, Issa NP, Rose SL, Ali A, Tao JX. Impact of periictal nurse interventions on postictal generalized EEG suppression in generalized convulsive seizures. *Epilepsy Behav*. 2016;*1*(58):22-25. https://doi.org/10.1016/j.yebeh.2016.02.025
10. Alexandre V, Mercedes B, Valton L, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. *Neurology*. 2015;*85*(18):1598-1603. https://doi.org/10.1212/WNL.0000000000001949
11. Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. *Epilepsia*. 2013;*54*(2):377-382. https://doi.org/10.1111/j.1528-1167.2012.03691.x
12. Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice. *Epilepsia*. 2004;*45*(8):993-996. https://doi.org/10.1111/j.0013-9580.2004.02304.x

Findings	Bias and limitations	Sackett's score and comments
Improvement Measures: The effect of oxygenation on sudden fatal audiogenic seizures in three mouse strains. Outcomes: Oxygenation completely prevented fatal seizures in all three mouse strains (treatment groups 2). This is in comparison with fatal seizures that occurred in 100%, 100% and 58% of the air-treated D2, B6SAS and primed-B6 mice (treatment groups 1), respectively. *p* value <.01 Oxygenation had no effect on incidence or severity of AGS. Other Outcomes: To assess long-term protective effects of oxygenation, some of the mice that survived in treatment group 2, from each mice strain, were tested 24 h later in either air (treatment groups 3) or oxygen (treatment groups 4) chambers. Majority of mice in treatment group 3 died; however, no mice in group 4 died. Again, no difference was found in AGS severity in either group. To assess short-term protective effects of oxygenation, mice from each strain were exposed to 2 min of oxygen 1 min prior to being tested (treatment groups 5). The majority of mice in this group died suddenly.	Sudden ictal death in humans may share some common mechanisms to sudden fatal AGSs in mice. However, it is not an exact model of mechanism or physiology Varying mice strains confound results due to variability in genetic predisposition to AGS and potential influence on oxygen efficacy No author's comments on potential limitations or introduction of bias	Sackett's score = 2b Oxygenation at time of AGS completely prevented sudden fatal AGSs in mice. Oxygenation had no protective effect on the incidence or severity of AGS Testing of treatment groups three and four suggested that oxygenation had no long-term protective effect in preventing fatal AGSs. Testing of treatment group five suggested that oxygenation had no short-term effect of preventing fatal AGSs as mice exposed to oxygen prior to AGS mostly died. Oxygen is most effective at the time of seizure Mechanisms of human sudden unexpected death in epilepsy (SUDEP) may be related to anoxia—which could be similar to the mechanisms in sudden fatal AGSs in mice. SUDEP usually occurs in sleep, and so patients at risk could wear oxygen masks to mitigate this risk Further tests are needed to test the possibility of therapeutic hypoxic conditioning with the aim of increasing hypoxic tolerance.

13. Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. *Lancet*. 1991;*337*:1175-1180.

How to cite this article: Smith AN, Abraham J, Shankar R. Oxygen for seizures, more questions than answers: A scoping review. *Acta Neurol Scand*. 2021;00:1–11. https://doi.org/10.1111/ane.13508

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

APPENDIX 1

LITERATURE SEARCH TERMS

Epilepsy Terms:

exp "SEIZURE, EPILEPSY AND CONVULSION"/

(convuls* OR seizure* OR epilep*).

Hypoxia Terms.

(hypoxia OR hypoxic).ti,ab.

(HYPOXIA OR BRAIN HYPOXIA OR HYPOXIC LUNG VASOCONSTRICTION OR INTERMITTENT HYPOXIA).

(anoxia OR anoxic OR anoxemia OR anoxemic).

(Hypoventilation).

(hyperventilation).

(hypoxemia OR hypoxemic OR hypoxaemia OR hypoxaemic).

Oxygen Therapy Terms.

exp "OXYGEN THERAPY"/

exp "OXYGEN DELIVERY DEVICE"/

(oxygenation OR Hyperbaric oxygen).

((treatment OR management OR administration OR therapy) ADJ2 oxygen).

(supplementary oxygen).